Title: Safety and efficacy of adenosine 5'-triphosphate as a hyperemic agent for the assessment of peripheral fractional flow reserve

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Running title: Comparison of vasodilators in the FFR of PAD

Abstract

Aim: The myocardial fractional flow reserve (FFR) is a useful measure of physiological stenosis in the coronary artery. Previous reports have identified peripheral FFR (pFFR) as another useful measure in peripheral artery disease (PAD); however, the vasodilators used to obtain maximal hyperemia varied among studies. The present study was conducted to identify the ideal vasodilator and vasodilator dose for pFFR assessment.

Methods:

We enrolled 24 patients with 26 lesions, comprising 14 lesions of the iliac artery and 12 lesions of the superficial femoral artery (SFA). After measuring the mean aortic pressure (Pa), the guidewire was advanced across the lesion and the mean distal pressure (Pd) was measured at the baseline Pd/Pa. A 100-μg dose of adenosine 5'-triphosphate (ATP) was then administered to

obtain a pFFR with a washout interval of 5 to 10 minutes. Next, 200 μg of ATP, 10 mg of papaverine hydrochloride, or 1.5 mg of isosorbide dinitrate was administered before the final pFFR measurement.

Results:

The baseline Pd/Pa (0.88 ± 0.08) was significantly decreased after each vasodilator ($P < 0.0001$), but there was no significant difference in pFFR among vasodilators ($P = 0.7569$). The study was discontinued in two patients with SFA lesions due to decreased systemic blood pressure after vasodilator administration.

Conclusions:

The hyperemic efficacy of 100 μg of ATP administered intra-arterially was similar to the efficacies of 200 μg of ATP, 10 mg of papaverine hydrochloride, and 1.5 mg of isosorbide

dinitrate. Given the milder side effects of ATP versus other vasodilators, an intra-arterial dose of ATP 100 μg may be optimal as a first-line agent for pFFR measurement.

Keywords: peripheral artery disease, endovascular treatment, fractional flow reserve, physiological stenosis, adenosine 5'-triphosphate

Introduction:

Stent implantation has improved the initial and long-term outcomes of endovascular treatment (EVT) in both the iliac artery and superficial femoral artery (SFA) in patients with peripheral artery disease (PAD). The TASC II guidelines recommend EVT for TASC A- & B-type lesions, which show short- or middle-length stenosis and short chronic total occlusion (1). While the ankle brachial index (ABI) and exercise ABI are established measures to evaluate ischemia in the whole limb of PAD patients, evaluating culprit lesions is sometimes very difficult in patients with multiple lesions or angiographically moderate stenotic lesions. EVT for non-significant stenotic lesions confers no symptomatic improvement and can induce harmful events.

The fractional flow reserve (FFR) is an established measure for estimating physiological stenosis in coronary artery disease (2).

The measurement and assessment of myocardium FFR is a useful procedure for reducing the rate of major adverse cardiovascular events in percutaneous coronary intervention (PCI) (3). Vasodilator administration to maximize hyperemia of the myocardium is key to the correct measurement of FFR. In coronary artery disease, intracoronary papaverine and intravenous adenosine 5'-triphosphate (ATP) are usually administered as vasodilators to induce maximal hyperemia when assessing diffuse coronary atherosclerosis (4).

In contrast, the EVT guidelines (1, 5) recommend pressure measurements across lesions both at rest and during hyperemia induction in cases with unclear hemodynamic significance of the target lesion. At the same time, several reports (6-15) have advocated peripheral FFR (pFFR) for evaluating the significance of stenosis versus that of peak systolic pressure or

95 catheter-derived pressure gradients; however the vasodilators
96 used varied among these studies, and there is no standard
97 vasodilator defined for obtaining maximal hyperemia. The
98 present study thus sought to identify the ideal vasodilator and
99 dose for measuring pFFR without side effects.
100
101 **Methods**
102 **Patient population**
103 This investigation was a retrospective, single center study
104 conducted at Showa University Fujigaoka Hospital including
105 adult patients (>20 years of age) with intermittent claudication or
106 critical limb ischemia who underwent lower extremity artery echo
107 or enhanced computed tomography. Patients suspected of having
108 significant stenosis of the iliac artery or SFA underwent EVT. In
109 cases of moderate stenosis, pFFR was performed to judge whether

it is significant stenosis or not. Patients with acute limb ischemia, TASC II type C or D lesions, no patent arteries below the knee, or lesions with more than 90% stenosis on angiography were excluded from this study. TASC II C & D lesions were defined as those with long or multiple stenosis and long chronic total occlusion with or without calcification. The 24 patients (26 lesions) who met the inclusion criteria were enrolled in the study from January 2012 to December 2016.

The institutional review board of our hospital approved the study protocol, and all patients provided informed consent.

pFFR measurement

EVT was performed under local anesthesia using a 4 or 6 French (Fr) guiding sheath (Parent Plus®, Medikit, Tokyo, Japan) for treatment introduced via the ipsilateral approach or a 6 Fr

125 guiding sheath (Destination®, Terumo, Tokyo, Japan) introduced
126 via the contralateral approach.
127 All patients received intravenous heparin (5000 U)
128 administration prior to placement of the guidewire. After
129 confirming 50-75% stenosis of either the iliac artery or SFA by
130 peripheral angiography, the tip of the guiding sheath was
131 confirmed to be at a position where the peripheral blood flow was
132 left undisturbed. A 0.014" pressure guidewire (St. Jude Medical,
133 St. Paul, MN, USA) was advanced to the distal tip of the guiding
134 sheath, the pressure was equalized, and then the mean aortic
135 pressure (Pa) was measured after a 5 to 10-mL saline flush to
136 remove contrast agent in the catheter. The guidewire was then
137 advanced across the lesion for measuring the mean distal
138 pressure (Pd) at baseline Pd/Pa (Fig. 1).
139 The optimal dose of papaverine hydrochloride for inducing

maximum hyperemia was assessed in a preliminary investigation, as different doses of the agent were used in previous studies (9, 10, 16). Hyperemia was induced with 10 mg of papaverine hydrochloride, the Pa and Pd measurements were repeated, and then pFFR was calculated as the ratio of mean Pd to mean Pa during hyperemia. While the pFFR thus calculated increased to 20 mg and 30 mg with a washout interval of 5 to 10 minutes between subsequent administrations, no significant difference in pFFR was found at different doses (Fig. 2). Therefore, the optimal papaverine hydrochloride dose for inducing hyperemia in this study was defined as 10 mg.

Three vasodilators were compared in the present study: ATP (7, 10), papaverine hydrochloride (8, 9, 10, 14), and isosorbide dinitrate. First, 100 μg of ATP was administered from the guiding sheath to determine the pFFR with a washout interval of 5 to 10

minutes. After confirming complete recovery to the baseline pFFR, 200 μg of ATP was administered. The same procedures were repeated after administration of 10 mg of papaverine hydrochloride and 1.5 mg of isosorbide dinitrate.

Statistical analysis

Continuous variables are expressed as means ± standard deviations and categorical variables are reported as percentages. Variable comparisons between groups were conducted using ANOVA & post hoc tests for continuous variables and Fisher's exact test for categorical variables. All analyses were performed using JMP software version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Table 1 details the characteristics of patients enrolled in this study. The patients had a mean age of 77 ± 1 (range 60-95) years and 18 patients were male (75.0%). Twenty patients (81.0%) had intermittent claudication and four (19.0%) had critical limb ischemia. Table 2 shows the types of lesions and procedures used. Of the 26 lesions, 14 (53.8%) were located in the SFA and 12 (46.2%) were located in the iliac artery; 7 (26.9%) lesions underwent balloon angioplasty, 17 (65.4%) underwent stent placement, and 2 (7.7%) were deferred for EVT based on the pFFR results.

Effects of each vasodilator

Figure 3 shows the baseline Pd/Pa and pFFR results for the vasodilators examined. The baseline Pd/Pa (0.88 ± 0.08) decreased

185 significantly after the use of every vasodilator ($P < 0.0001$), but
186 there was no significant difference in the level of decrease among
187 the vasodilators ($P = 0.7569$).
188
189 **Vasodilator side effects**
190 The study had to be discontinued in two patients with SFA
191 lesions due to decreases in systemic blood pressure after
192 vasodilator administration. In one case, the systolic blood
193 pressure dropped to 60 mmHg after the administration of 10 mg
194 papaverine hydrochloride, while in the other, the systolic blood
195 pressure dropped to 58 mmHg after the administration of 1.5 mg
196 isosorbide dinitrate.
197
198 **Discussion**
199 This is the first report comparing the effectiveness with which

maximum hyperemia can be measured using various agents for the assessment of pFFR in PAD. The intra-arterial administration of ATP, papaverine chloride, and isosorbide dinitrate demonstrated similar effects in obtaining maximum hyperemia in pFFR, but the latter two agents induced systemic drops in blood pressure in two patients. Regarding the dose of ATP, a 100 μg dose of ATP was effective in achieving maximum hyperemia.

The maximum blood flow reserve of skeletal muscle is greater than that of the myocardium (11); however, the muscle mass of the lower limbs varies much more between individuals compared to heart muscle, and the optimal vasodilator dose for obtaining maximum hyperemia depends on muscle mass (12, 13). In addition, the degree to which a vasodilator expands a blood vessel might also differ from person to person. For these reasons, it is

more difficult to determine the appropriate dose and type of vasodilator in pFFR than it is to measure FFR in PCI. Significant stenosis was traditionally defined physiologically as a mean arterial pressure difference greater than 10 mmHg (17), although passing a catheter through a lesion also induces a pressure gradient, even when using a small catheter such as a 4 Fr. Thus, a 0.014-inch pressure wire is superior to a small-size catheter in assessing the actual pressure gradient induced (6). In the present study we confirmed that the tip of the guiding sheath was placed at a position where the peripheral blood flow was left undisturbed on peripheral angiography. If the systolic pressure of the catheter became lower than that of the brachial pressure, we moved the catheter to a more proximal position, but not to a degree that would result in any difference between the sites. Papaverine has been reported to induce potential side effects such

as hypotension, variable patient response (16, 18), and serious arrhythmia (19). In addition, intra-coronary papaverine can prolong the QT interval, leading to polymorphic ventricular tachycardia and ventricular fibrillation. Although the mechanism underlying papaverine-induced QT prolongation is not fully understood, the drug can inhibit delayed rectifying potassium currents (IKr) and prolong the action potential duration. When the action potential duration is excessively prolonged, premature after-depolarization could provoke triggered activity and subsequent ventricular fibrillation (19). Approximately half of all PAD patients are complicated with ischemic heart disease, so precautions to protect patients from serious arrhythmias are imperative. Thus, this study had to be discontinued in two patients with SFA lesions because of decreases in systemic blood pressure after receiving 10 mg of papaverine chloride or 1.5 mg of

245 isosorbide dinitrate. Two of four patients taking beta-blockers in
246 this study were also discontinued due to a decrease in systemic
247 blood pressure. The administration of adenosine triphosphate 100
248 µg and 200 µg elicited no such decrease. The very short half-life (1
249 to a few seconds) of ATP makes it a useful agent for repeated
250 evaluations of ischemia in multiple arteries without side effects
251 (20).

252 In this preliminary study we determined that a 10 mg dose of
253 papaverine hydrochloride was optimal for obtaining maximum
254 hyperemia. The difference in the hyperemic dose of papaverine
255 hydrochloride versus that was reported by Miki et al. (16) may
256 stem from differences in the target patients and vessels, as their
257 study involved SFA lesions of normal subjects. Further, patients
258 receiving papaverine hydrochloride have shown variable
259 responses to the agent. Meanwhile, the 1.5 mg dose set for

isosorbide dinitrate was based on empirically administered amounts in Japan. Finally, we set the ATP dose at 100 μg and 200 μg in the present study, based on a dose of 1 μg/kg in an earlier study and 200 μg in another study (7, 10).

Conclusions

The hyperemic efficacy of the intra-arterial administration of 100 μg of ATP was similar to the efficacies of 200 μg of ATP, 10 mg of papaverine hydrochloride, and 1.5 mg of isosorbide dinitrate. Given the milder side effects of ATP versus other vasodilators, ATP at an intra-arterial dose of 100 μg may be optimal as a first-line agent for pFFR measurement.

Conflict of interest disclosure: None.

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Figure legend

Fig. 1. pFFR measurement of a mildly stenotic lesion in the left external iliac artery.

A: The delta shows mild stenosis of the left external iliac artery.

B: The pressure guidewire at the distal tip of the guide sheath measures the mean aortic pressure (arrow).

C: The pressure guidewire at the distal tip of the stenosis lesion measures the mean distal pressure (arrow).

pFFR, fractional flow reserve in peripheral artery disease

Fig. 2. pFFR following each papaverine hydrochloride dose (8 lesions).

388 pFFR, fractional flow reserve in peripheral artery disease

389

390

391 Fig. 3. Baseline Pd/Pa and pFFR obtained with each vasodilator

392 (24 lesions).

393

394 Pd, mean distal pressure. Pa, mean aortic pressure. pFFR,

395 fractional flow reserve in peripheral artery disease

396

Table 1. Patient characteristics (26 lesions and 24 patients)	
Variable	
Age, years	77±1
Sex, male (%)	18 (75.0)
BMI, kg/m2	21.2±5.0
Hypertension (%)	20 (83.3)
Diabetes mellitus (%)	8 (33.3)
Insulin use (%)	2 (8.3)
Dyslipidemia (%)	16 (66.7)
Current smoker (%)	5 (20.8)
Past smoker (%)	9 (37.5)
Coronary artery disease (%)	13 (54.2)
Cerebral vascular disease (%)	2 (8.3)
Hemodialysis (%)	4 (16.7)
Clinical presentation	
Intermittent claudication (%)	20 (81.0)
Critical limb ischemia (%)	4 (19.0)
Fontaine	
I (%)	0 (0)
II (%)	20 (81.0)
III (%)	0 (0)
IV (%)	4 (19.0)
Rutherfold	
1 (%)	0 (0)
2 (%)	9 (28.6)
3 (%)	11 (52.4)
4 (%)	0 (0.0)
5 (%)	4 (19.0)
6 (%)	0
Medications	
Aspirin (%)	15 (62.5)
Clopidogrel (%)	12 (50.0)
Cilostazol (%)	8 (32.3)
Sarpogrelate (%)	4 (16.7)
Statin (%)	10 (41.7)
ACE/ARB (%)	11 (45.8)
Ca blocker (%)	10 (41.7)
β-blocker (%)	4 (16.7)
ACE: Angiotensin converting enzyme inhibitor	
ARB: Angiotensin II receptor blocker	

Table 2. Characteristics of the lesions and procedures used (26 lesions)

Variable	
Lesion characteristics	
SFA (%)	14 (53.8)
Iliac (%)	12 (46.2)
TASC classification	
A (%)	14 (53.8)
B (%)	12 (46.2)
Restenosis (%)	2 (7.7)
Vessel calcification (%)	10 (41.7)
Interventional results	
POBA (%)	7 (26.9)
STENT (%)	17 (65.4)
Deferred (%)	2 (7.7)
Number of stents	1.1±0.3
Total stent length (mm)	45.3±14.9
Mean stent diameter (mm)	7.7±1.0
Number of run-off vessels	
0 (%)	1 (3.8)
1 (%)	6 (23.1)
2 (%)	10 (38.5)
3 (%)	9 (34.6)

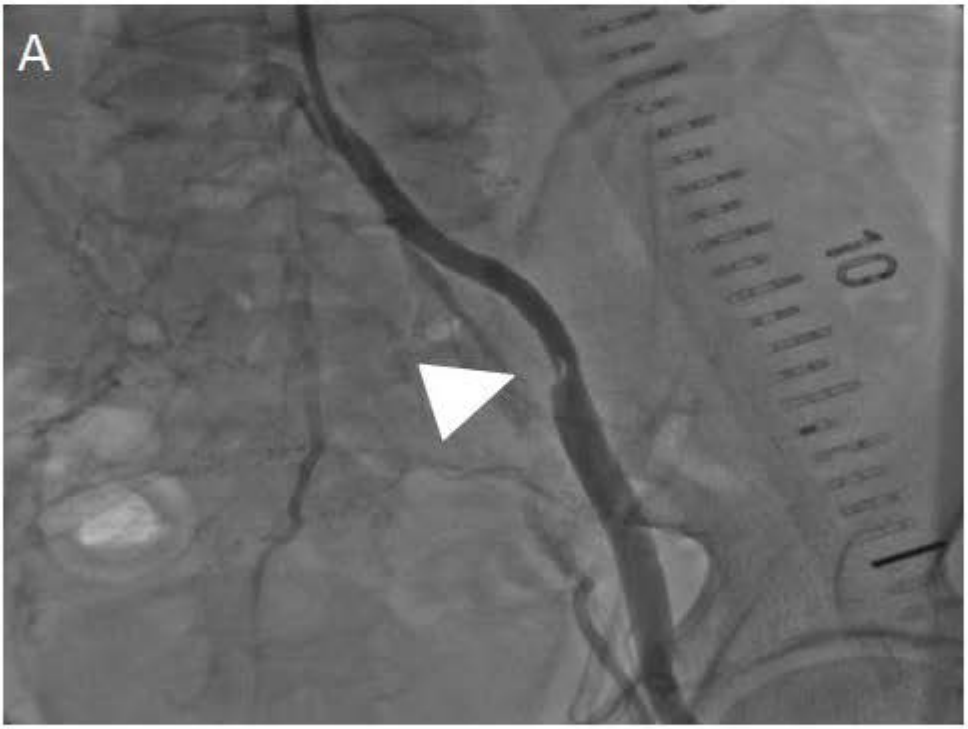
TASC: TransAtlantic InterSociety Consensus
SFA: Superficial femoral artery
POBA: Plain old balloon angiography

399

400

FIG1

401



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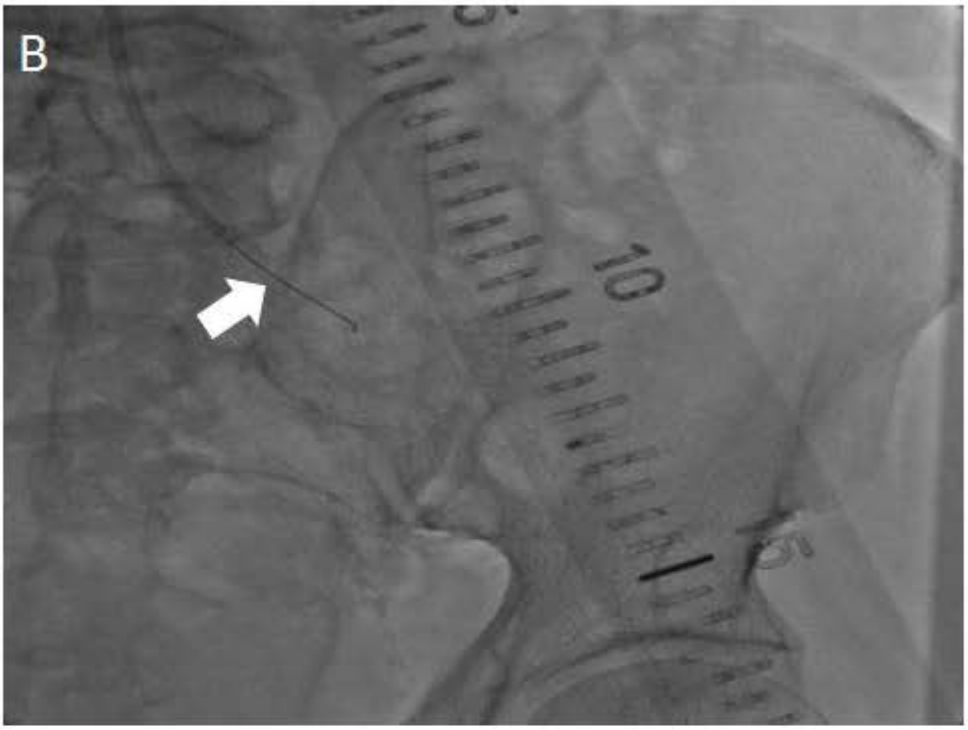

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FIG2

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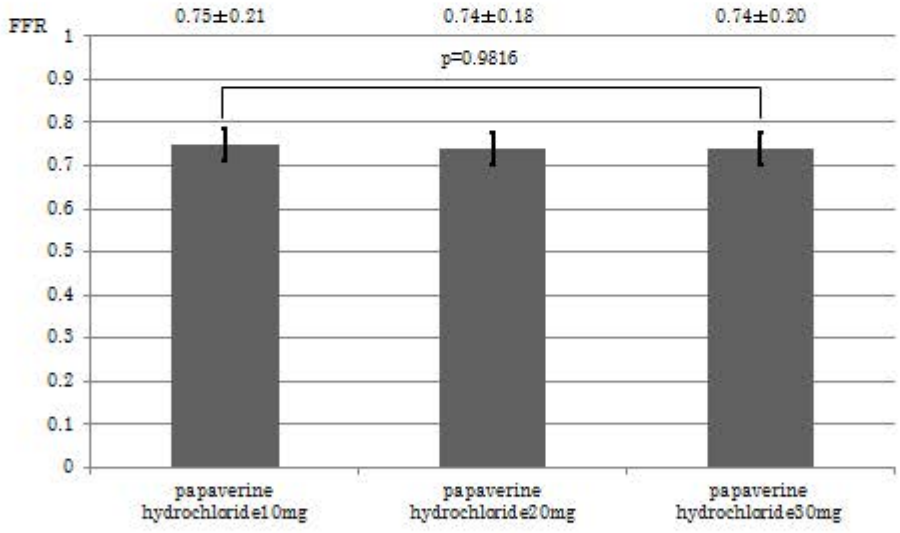
FFR
0.75±0.21
0.74±0.18
0.74±0.20
p=0.9816
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
papaverine hydrochloride10mg
papaverine hydrochloride20mg
papaverine hydrochloride30mg

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FIG3

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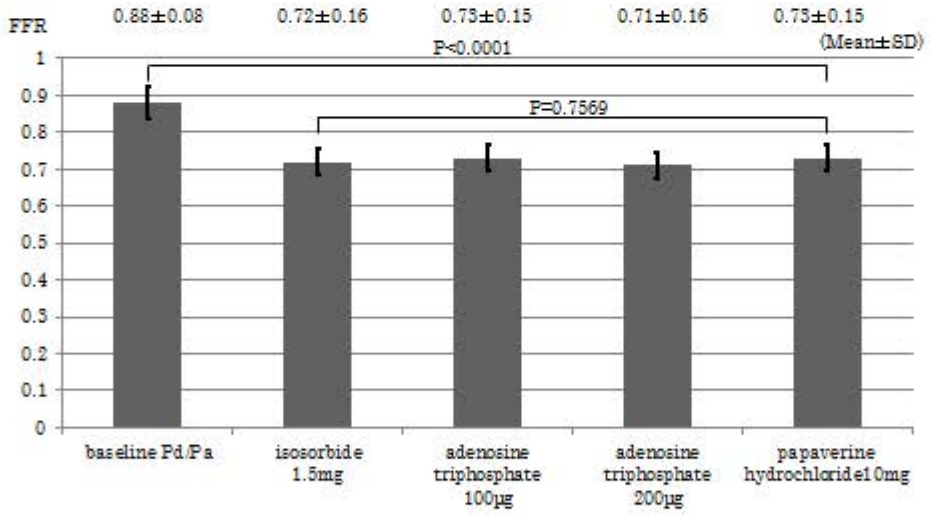
FFR
0.88±0.08
0.72±0.16
0.73±0.15
0.71±0.16
0.73±0.15
(Mean±SD)
P<0.0001
P=0.7569
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
baseline Pd/Pa
isosorbide 1.5mg
adenosine triphosphate 100μg
adenosine triphosphate 200μg
papaverine hydrochloride10mg

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